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Introduction

This addendum to the final report contains a summary of the data analyses for the research project entitled “Artificial Pancreas for Control of BG and Insulin Levels in Hospitalized Patients with Diabetes and Stress Hyperglycemia”, (Principal Investigator: Jeffrey Joseph, DO; Award Number: W81XWH-04-1-0004). The original tasks set forth in the statement of work for this research project are given in Table 1 (modifications to the statement of work appear in italics). The information herewith addresses tasks 3 and 4. Please refer to the original final report submitted February 2007 for information on all other tasks.

The body of the report is separated into two sections. Section A will review the performance of the needle-type interstitial fluid glucose sensor, the Telemetered Glucose Monitoring System (TGMS). Six TGMS sensors were placed on each of the ten subjects studied for a total of 60 sensors. Section B will review the performance of the vascular blood glucose sensor, the Vascular Glucose Monitoring System (VGMS). A total of five sensors were studied with one sensor inserted into a central vein in the first five subjects.

Table 1: Statement of Work

Task	Description
1	Arrays of needle-type glucose sensors will be developed for the real-time monitoring of ISF glucose levels in hospitalized patients with type 1 and type 2 diabetes. ISF glucose sensors will be modified in collaboration with Medtronic-MiniMed scientists to provide continuous monitoring of the six output signals. Two 3-sensor arrays will be combined (sensor hardware, cables, software, portable PC) to provide real-time recording and display of six simultaneous sensor output signals. Custom software will be developed to record detailed clinical/chemistry data in real-time at the bedside. *The eligible patient population was broadened to include non-diabetic patients undergoing a pancreatectomy.*
2	A human clinical study will be performed to investigate the correlation between sensor output and blood glucose levels in hospitalized patients with type 1 (n= 5) and type 2 (n=5) diabetes. Sensor arrays will be inserted into the subcutaneous tissue of the abdomen (3-sensor array) and upper arm (3-sensor array) prior to anesthesia and surgery. Six sensor output signals will be recorded over a 60-hour pre-op, intra-op, and post-operative period. Sensor signals will be compared to reference blood glucose measurements simultaneously sampled from arterial, capillary, and venous blood (every 20 to 60 minutes). Detailed clinical and blood/urine chemistry data will be entered into a PC database by a bedside vigilant observer. *The eligible patient population was broadened to include non-diabetic patients undergoing a pancreatectomy. The subpopulation sample sizes (i.e., 5 patients with type 1 diabetes and 5 patients with type 2 diabetes) were removed. The chest and thigh were added as sites for sensor insertion. The frequency of arterial blood sampling was every 20 minutes for 36 hours, the frequency of venous blood sampling was every 60 minutes (which coincided with every third arterial sample) for 60 hours, and the frequency of capillary blood sampling was every 3 hours (which coincided with every third venous sample) for 60 hours. Clinical and blood/urine chemistry data was recorded long-hand at the bedside and transcribed into a electronic spreadsheet after the conclusion of the study.*
3	The above data set will be studied to determine the effects of averaging, smoothing, and correlating multiple (6) ISF sensor output signals on the accuracy, precision, robustness, and noise of the sensor array as a possible input to the artificial pancreas (AP) computer controller. The accuracy of ISF sensor glucose measurements will be evaluated as a function of the number of simultaneously measured ISF sensor outputs signals. The correlation after fault-analysis of one or more sensors within a two- to six-sensor array will be investigated.
4	The above data set will be studied to determine the optimal frequency and timing of sensor re-calibration in the hospital setting. The time-dependent behavior of the ISF sensors will be modeled. Modeling ISF sensor array behavior may allow us to predict sensor drift and make automatic adjusts in the calibration coefficient, in order to decrease the need for frequent reference blood samples. We plan to determine the relationship between sensor accuracy and frequency of re-calibration, based upon a retrospective analysis of ISF glucose sensor data and reference blood glucose (BG) data. We also plan to determine how the timing of sensor recalibration (during a period of glucose level stability versus a period of instability) affects sensor array accuracy in relation to reference BG measurements. Fault prediction methods will be developed to permit the identification (and subsequent removal) of an individual ISF sensor signal from a sensor array that does not follow the defined behavior of a stable and nominal sensor.
5	The detailed database of clinical information (vital signs, inputs & outputs, timing of medications, fluids, procedures, and meals) and blood chemistry data, (blood glucose, lactate, pH, PaCO2, PaO2, SaO2, fatty acids, insulin, electrolytes, BUN, hematocrit) will be studied to understand the clinical conditions that occur during nominal sensor function, dysfunction, and failure. This database will be used in the future by Jefferson, Drexel, and Medtronic-MiniMed scientists to develop a robust computer control algorithm for the in-hospital AP system.

Body

In order to quantify the performance of the continuous glucose sensors, the Pearson Product Moment Correlation (designated by the letter R) and the Mean Absolute Relative Deviation (MARD) were calculated. The formulations for these two measures are:

$$R = \frac{\sum xy - \frac{1}{n}\sum x \sum y}{\sqrt{\left(\sum x^2 - \frac{1}{n}\left(\sum x\right)^2\right)\left(\sum y^2 - \frac{1}{n}\left(\sum y\right)^2\right)}} \quad \text{and} \quad MARD = \frac{1}{n}\sum \frac{|x-y|}{x}$$

where *x* and *y* are paired values of the reference and sensor glucose readings, respectively, and *n* is the number of paired values.

As per the protocol, reference blood samples were obtained every 20, 60, and 180 minutes for arterial, venous, and capillary blood, respectively. Duplicate measurements were performed on each arterial and venous blood sample. On occasion, coagulation of the sample or reference device malfunction prevented duplicate measurements – 14% and 16% of arterial and venous samples were not tested in duplicate. These measurements were not included in the subsequent analysis. If duplicate glucose measurements were not within 10% of each other, these measurements were also discarded. Otherwise, the duplicate measurements were averaged and the average was used in the subsequent analysis. For capillary reference measurements, only one measurement was performed for each sample and all capillary measurements were included in the subsequent analysis.

To generate the paired values used in the calculation of R and MARD, the closest sensor measurement in time was paired with each valid reference measurement. If the time difference exceeded 2.5 minutes, the paired data were not included in subsequent analysis.

Section A

Run-in Time Analysis

The Medtronic Diabetes TGMS sensor is a needle-type glucose sensor that is placed in the subcutaneous tissue. After implantation, a period of time is required for the sensor's output signal to stabilize. This period is referred to as the sensor's run-in time. Medtronic scientists working with the TGMS technology report a run-in time of 2-3 hours.

Purpose

Run-in analyses were performed to determine the optimal run-in time in this study population. Sensor data collected during the run-in period is excluded from subsequent analysis.

Methods

Individually estimated R values for each sensor were modeled in a linear mixed-effects model [Vonesh 1997] that incorporated random effects of subject and sensor. Analyses evaluated correlation between time-matched raw sensor output and arterial reference values, which provided most frequently sampled pairs. Outliers were identified by examining the residuals and random effect estimates and applying the boxplot outlier detection rule [Hoaglin 1986]. The confidence intervals for the average R values were computed from the mixed effects models fitted to outlier-free data.

Results

Figure 1 shows the individual R values for all TGMS sensors group by subject. Four sensors were identified as outliers (Table 2). These sensors had inconsistently lower correlation between the raw sensor output and arterial reference across all run-in times. These sensors were excluded from the model used for evaluation of average sensor performance and optimal run-in time. Figure 2 depicts the average R by run-in time. No run-in time (run-in time zero) yielded significantly lower average R as compared to all other run-in times from 1 to 6 hours ($p<0.001$ in every case). Similarly, the 1-hour run-in time yielded significantly lower average R as compared to run-in times from 2 to 6 hours ($p<0.001$ in every case). For the 2-hour run-in time, the pair-wise differences in R were not significant, except for the difference of -0.038 between the 2- and 6-hour run-in time ($p=0.037$).

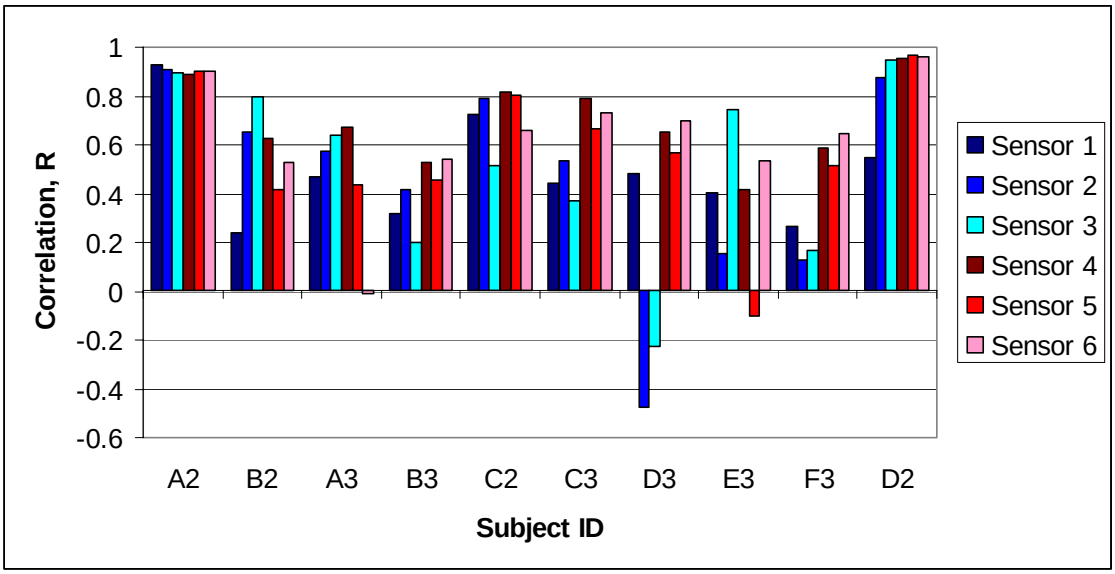


Figure 1: R values for TGMS sensors using a 2-hour run-in time

Table 2: TGMS sensors identified as outliers in the mixed-model analysis of run-in time (average R values included for comparison)

		Run-in Time						
Subject ID	**Sensor**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
A3	6	-0.220	-0.165	-0.008	-0.015	-0.017	-0.003	0.062
D3	2	-0.477	-0.477	-0.477	-0.477	-0.477	-0.477	-0.477
D3	3	-0.226	-0.226	-0.226	-0.226	-0.226	-0.226	-0.226
E3	5	-0.417	-0.035	-0.099	-0.437	-0.561	-0.476	-0.476
average R for all other sensors		*0.432*	*0.514*	*0.601*	*0.624*	*0.628*	*0.631*	*0.639*

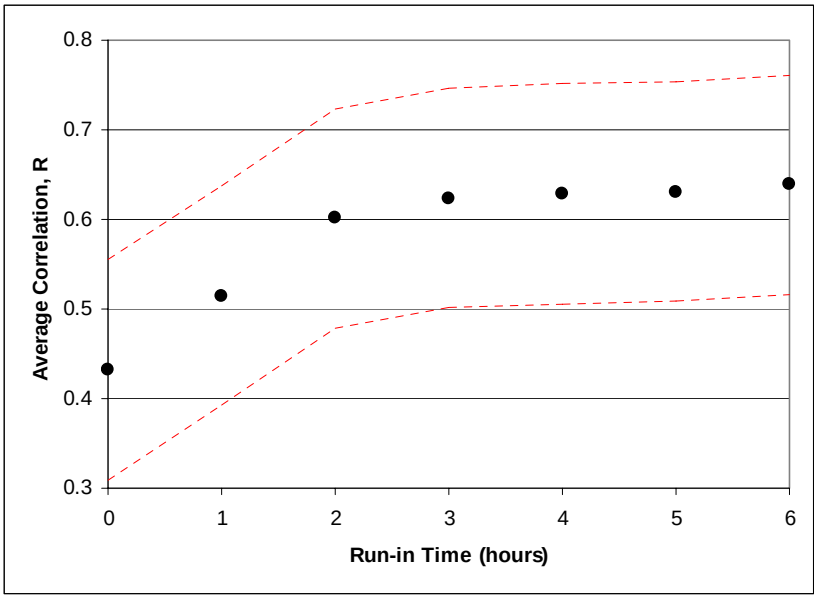


Figure 2: Average correlation (solid blank circles) with 95% confidence intervals (dashed lines) between paired TGMS sensor and reference arterial measurements for run-in times of 0, 1, 2, 3, 4, 5 and 6 hours

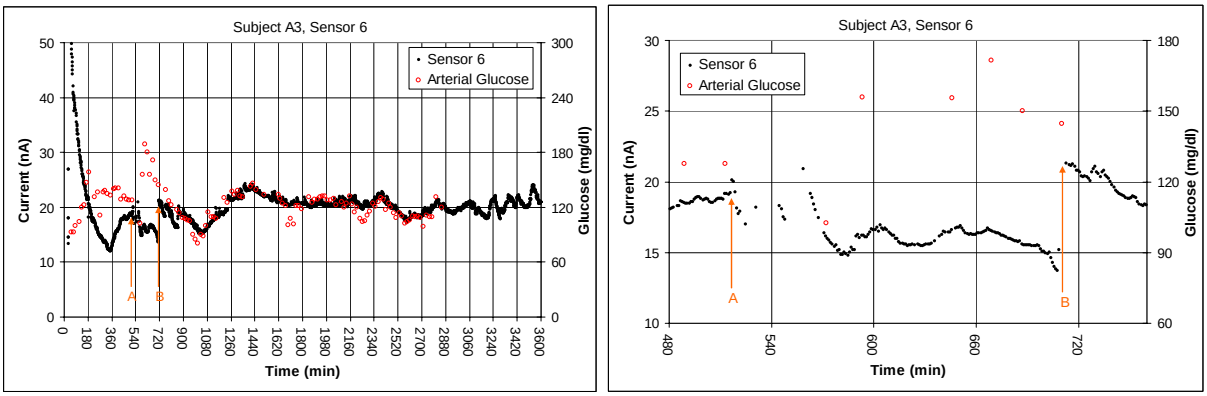
Discussion

The tradeoff between the availability of data following sensor insertion and the quality of that data is illustrated in Figure 2. The increase in average value of R from no run-in time to a run-in time of 1 hour was 19%, from a 1-hour run-in time to a 2-hour run-in time was 17%, from a 2-hour run-in time to a 3-hour run-in time was 3.8%, from a 3-hour run-in time to a 4-hour run-in time was 0.6%, from a 4-hour run-in time to a 5-hour run-in time was 0.5%, and from a 5-hour run-in time to a 6-hour run-in time was 1.3%. For this study, a significant improvement in R is obtained by excluding the first two hours of TGMS sensor data[*].

Understanding the cause of the abnormal behavior for the four outlying sensors listed in Table 2 is just as important as the characterizing the normal behavior of the sensors. TGMS sensor 6 from subject A3 was inserted into the lower right chest. At the time of removal, the sensor's base had good adhesion to the skin; traces of blood were observed on the sensor tip and base; and active bleeding occurred at the insertion site immediately after the sensor was removed. Figure 3 depicts data for sensor 6 along with the reference arterial glucose data. Starting at time point A (~510 minutes post sensor insertion), there are significant losses of data. This point corresponds to the time that the subject awaked from general anesthesia and was transferred to the Surgical Intensive Care Unit. At time point B (~700 minutes post sensor insertion) a large jump in the sensor trajectory occurred. The clinical assessments of the subject before and after time point B indicate the subject transitioned from sleep to wakefulness during this time. A change in local tissue perfusion around the sensor, change in tissue oxygen tension, or gross sensor movement may have caused this shift in the sensor's output. When the pairwise sensor/reference points (Figure 4) are plotted, two unusual regions are apparent. Points in region C correspond to the data collected within the first two hours of the study. Points in region D correspond to the data collected between times A and B (described above). If all paired data

[*] Medtronic's commercial product, Guardian RT, applies a mild electric current to the sensor to reduce the length of the run-in period to one hour. This feature was not used in the current study.

is excluded up to time point B (*i.e.*, a 12-hour run-in time), the correlation for sensor 6 is 0.703 (compared to -0.008 for the 2-hour run-in time). Developing methods to (1) identify a sustained shift (versus a transient spike) in the sensor's signal and (2) mitigate its effect could improve sensor performance.



A B

Figure 3: Sensor and reference arterial data for Subject A3 (t=0 is the time when the sensor was inserted). Panels A and B represent the data for the entire study period and a 300-minute period starting 420 minutes after sensor 6 was inserted, respectively. See text for explanation of time points A and B.

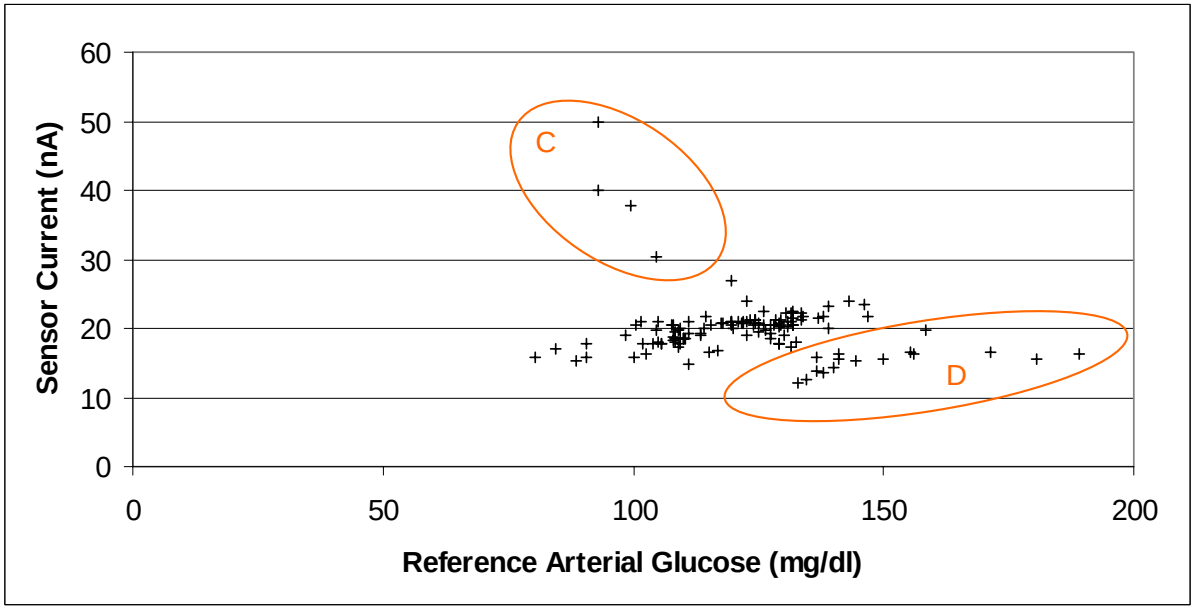


Figure 4: Pairwise sensor/reference data for subject A3. See text for explanation of regions C and D.

Gross sensor movement may also explain the exclusion of TGMS sensors 2 and 3 for subject D3. Figure 5 is a photograph of TGMS sensors 1-3 (sensor array 1) *in situ* immediately before explantation. The photo demonstrates the crowded milieu in which these investigational devices were placed. Wires associated with the clinical monitoring (CVP and ECG) of the subject crisscross over the sensor array. Any one of these wires could have easily caught and pulled the sensor transmitters. Each sensor lies directly beneath its respective transmitter. When the

sensors were removed at the end of the study, sensor 1 was complete dislodged, and sensor 2 was partially dislodged. Although sensor 3 was still fully implanted, it is probable that all sensors in this array experience significant movement throughout the study, leading to a degradation in sensor performance.

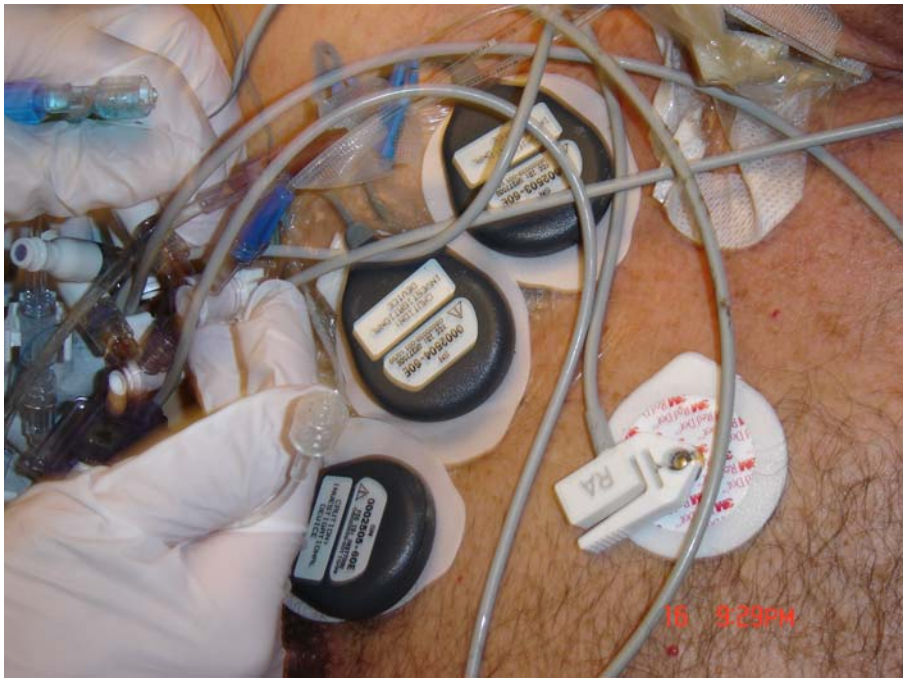


Figure 5: TGMS sensor array 1 (sensors 1, 2 and 3) *in situ* on subject D3 at the end of the study. Each transmitter is placed in close proximity to the sensor (upper right – sensor 1 transmitter; middle – sensor 2 transmitter; lower left – sensor 3 transmitter). Also pictured are the central venous pressure sensor/wires and sampling port for reference blood samples (far left) and the RA ECG pad (bottom right) and several gray ECG wires.

For TGMS sensor 5 on subject E3, there is no obvious reason for the sensor's poor performance. Reference arterial glucose concentration quickly rose from a preoperative value of 103 mg/dl to a maximum value of 218 mg/dl 180 minutes after TGMS sensor 5 was placed in the subcutaneous tissue of the lateral right thigh. After peaking intraoperatively, the arterial glucose concentration slowly fell back toward its preoperative value (Figure 6, Panel A). When the first two hours of data are excluded, no discernable correlation is observed between the sensor output and the reference arterial glucose levels (Figure 6, Panel B). No mechanical issues (e.g., poor adhesion, significant bleeding) were observed at the time of sensor explantation. Subject E3 had the second lowest BMI (20.7 kg/m^2) out of the 10 subjects (range: 19.1 – 46.1 kg/m^2) and the sensor could have been placed in muscle as opposed to adipose tissue However, this is only speculation and cannot be verified.

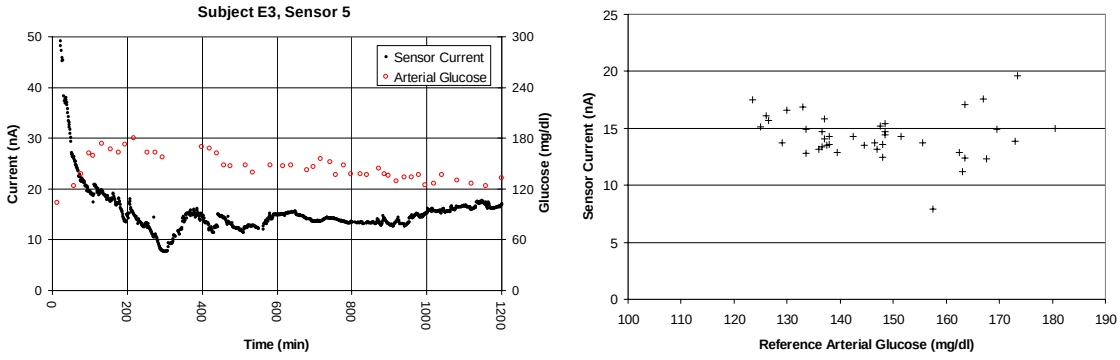


Figure 6: TGMS sensor 6 and reference arterial data for Subject E3. The time course of the sensor output (nA) and the reference arterial glucose concentration (mg/dl) is shown in Panel A (t=0 is the time when the sensor was inserted). The pairwise sensor/reference data points excluding those collected in the first 2 hours is shown in Panel B.

Regression Analysis

The recalibration analysis presented in the next section uses a one-point calibration routine with a fixed offset. The scientists at Medtronic Diabetes report a 2nA current when no glucose is present (0mg/dl). Linear regression analysis was performed to estimate the slope (m) and intercept (b) from the equation y = mx + b where y is the sensor output in nanoamps and x is the reference arterial glucose concentration in milligrams per deciliter. The estimate of the y-intercept was use to verify the value of the offset in the study population.

Purpose

Regression analysis was performed to verify the appropriate offset for the calibration routine used in subsequent analysis.

Methods

The linear relationship between each sensor output and reference arterial blood glucose measure was evaluated by fitting robust linear regression lines. Sensors identified previously as outliers in the determination of run-in time (Table 2) were excluded from analysis. Paired sensor/reference data collected within the first two hours (run-in time) were not used in the analysis. Robust curves were fitted in SAS using robust mixed model estimator of linear regression parameters [Yohai 1987]. Slopes and intercepts of robust regression lines are minimally affected by outliers that are present in these data due to the noisy sensor signals. The resulting individually estimated sensor-specific slopes and intercepts were modeled separately in a linear mixed-effects model [Vonesh 1997] that incorporated between-subject and between-sensor variability. Outliers were identified by examining the residuals and random effect estimates and applying the boxplot outlier detection rule [Hoaglin 1986]. The confidence intervals for the mean slope and intercept were computed from the mixed effects models fitted to outlier-free data.

Results

The individual estimates of y-intercept from robust regression lines ranged from -29.15 to 28.18 with the mean 4.24 and the median 5.43. Examination of residuals from the initial second stage

mixed effects model revealed four more outlier sensors with inconsistently high or low intercepts (Table 3). These sensors were removed from further second stage analysis of intercepts.

Table 3: TGMS sensors identified as outliers in the estimation of the y-intercept for the linear regression analysis.

Subject	Sensor	Y-intercept Estimate	Lower Confidence Limit	Upper Confidence Limit
B2	5	19.00	15.03	22.98
D2	3	-10.24	-11.82	-8.66
E3	2	28.18	21.10	35.26
E3	3	-29.15	-42.22	-16.07

From the second stage mixed effects model, based on outlier-free data, the average intercept was 4.04 (95% CI: 0.30, 7.78). The average intercepts for each subject are listed in Table 4.

Table 4: Subject-specific average y-intercept calculated from outlier-free data

	Average	95% Confidence Limits	
Subject	Y-intercept	Lower	Upper
A2	5.49	1.15	9.83
A3	7.86	3.36	12.35
B2	5.1	0.61	9.6
B3	11.51	7.17	15.85
C2	-0.01	-4.34	4.33
C3	7.57	3.24	11.91
D2	1.75	-2.75	6.24
D3	-4.99	-9.7	-0.28
E3	2.72	-2.31	7.75
F3	3.38	-0.96	7.72

The estimates of slope ranged from -0.070 to 0.323 with the mean 0.104 and the median 0.097. Examination of residuals from the second stage mixed effects model revealed two outlier sensors (Table 5). These sensors were removed from further second stage analyses of slopes.

Table 5: TGMS sensors identified as outliers in the estimation of the slope for the linear regression analysis.

Subject	Sensor	Slope Estimate	Lower Confidence Limit	Upper Confidence Limit
E3	2	-0.070	-0.118	-0.022
E3	3	0.323	0.235	0.412

From the second stage mixed effects model, based on outlier-free data, the average slope was 0.104 (95% CI: 0.086, 0.122). The subject-specific estimated average slopes are listed in Table 6.

Table 6: Subject-specific average slope calculated from outlier-free data

Subject	Average Slope	95% Confidence Limits Lower	Upper
A2	0.097	0.071	0.122
A3	0.085	0.059	0.112
B2	0.091	0.066	0.116
B3	0.099	0.074	0.125
C2	0.115	0.089	0.140
C3	0.087	0.062	0.112
D2	0.129	0.104	0.154
D3	0.132	0.105	0.160
E3	0.100	0.071	0.130
F3	0.101	0.076	0.126

Discussion

The estimate of the fixed offset (*i.e.*, y-intercept) was higher than the value reported by the manufacturer (4.04nA *vs.* 2.0nA). However, the manufacturer offset is well within the 95% confidence interval (0.30 - 7.78) determined by our analysis. There is no compelling evidence to alter the offset value for the subsequent recalibration analysis.

The population estimate of the slope was 0.104 (95% CI: 0.086, 0.122). Its inverse is the calibration coefficient used to transform the sensor output (I_s) into an estimate of blood glucose (G_s) such that $G_s = (I_s - b)/m$. Given the 95% confidence interval for m, the scaling coefficient (in mg dl^{-1} nA^{-1}) is expected to fall within the range of between 8.2 and 11.6.

Two groups of outliers were identified in this analysis, four outliers in the y-intercept determination (Table 3) and two outliers in the slope determination (Table 5). When combined, the resulting set of outliers consists of four unique sensors.

Recalibration Frequency Analysis

The output signal of the TGMS sensor needs to be scaled to represent plasma glucose concentration. The output signal is transformed using a single point calibration with a fixed offset in the form:

$$G_s = (I_s - b)/m$$

where I_s is the sensor output in nA, m and b are coefficients of calibration (scale and offset), and G_s is the resulting sensor estimate of the blood glucose concentration. The offset, m, is fixed at 2nA (see previous section for justification) and the scale, m, is calculated using a single time-matched pair of sensor and reference measurements. The calibration of the sensor signal is susceptible to noise in either the sensor or reference measurements. Filtering the sensor signal is possible because it has a relative high frequency of sampling while duplicate measures of the (arterial and venous) reference samples were used to identify and discard possible outliers in the reference data. Since the sensitivity of the sensor may change over time, recalibrations may be necessary to maintain an acceptable level of performance. The effect of recalibration frequency on R and MARD was investigated to determine a frequency that would result in MARD less than 0.2 and R greater than 0.9.

Purpose

Recalibration frequency analysis was performed to verify the appropriate recalibration timing.

Methods

Sensors identified as outliers in the Run-in Time and the Regression analyses were excluded from the Recalibration analysis (see Table 2 and Table 3). TGMS sensor data were smoothed using a 7th order FIR filter with coefficients [0.06598 0.20952 0.08470 0.13980 0.13980 0.08470 0.20952 0.06598]. Paired sensor/reference data collected within the first two hours (run-in time) were not used in the analysis. Intervals between recalibrations of 3, 6, 9, 12, 15, 24, 30 and 60 hours were investigated. For all recalibration intervals, R and MARD were computed for the same set of paired sensor and reference values which excluded the points used for recalibration every 3 hour. Individually estimated R and MARD values for each sensor were modeled in a linear mixed-effects model [Vonesh 1997] that incorporated random effects of subject and sensor. Outliers were identified by examining the residuals and random effect estimates and applying the boxplot outlier detection rule [Hoaglin 1986]. The average R and MARD values (±SD) were computed from outlier-free data for each recalibration interval.

Results

Four sensors (B2-1, C3-1, D2-1, D3-1) were identified as outliers with inconsistently lower correlation between the sensor output and arterial reference across all recalibration frequencies. Four sensors (B2-1, C2-6, C3-1, D3-1) were identified as outliers with inconsistently high MARD across all recalibration frequencies. Paired data with reference venous measurements from subjects B2 and C2 were not used in the calculations of MARD and R. Blood samples from the central venous catheter for subject B2 were unobtainable after only 13 hours. Sampling from the central venous catheter of subject C2 was stopped after 20 hours at the insistence of the subject's family. The data from this group of five unique sensors were excluded from the calculation of average sensor performance with different recalibration frequencies (Table 7).

Table 7: Average MARD and R values using arterial and venous reference data for recalibration intervals from 3 to 60 hours

	Arterial Reference				**Venous Reference**			
Recalibration	**MARD**		**R**		**MARD**		**R**	
Interval (hr)	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*	*mean*	*SD*
3	0.137	0.067	0.630	0.282	0.178	0.112	0.492	0.367
6	0.180	0.090	0.542	0.362	0.197	0.076	0.412	0.383
9	0.198	0.121	0.423	0.447	0.219	0.095	0.402	0.338
12	0.222	0.099	0.395	0.446	0.239	0.111	0.358	0.369
15	0.233	0.099	0.402	0.441	0.263	0.139	0.312	0.346
24	0.294	0.123	0.462	0.408	0.265	0.104	0.430	0.301
30	0.310	0.121	0.431	0.411	0.337	0.240	0.255	0.382
60	0.339	0.134	0.656	0.222	0.356	0.125	0.486	0.255

MARD decreased as the frequency of recalibrations increased (Figure 7A). Recalibrations performed every 6 hours resulted in an average MARD value below 0.2 for both venous and arterial reference datasets. The relationship between R and the recalibration frequency was not linear (Figure 7B) but was similar for both the venous and arterial datasets. On average, the best correlation between the sensor and reference data occurred when only one calibration was performed. As the recalibration frequency was increased, R decreased until the frequency of 1 recalibration every 6 hours.

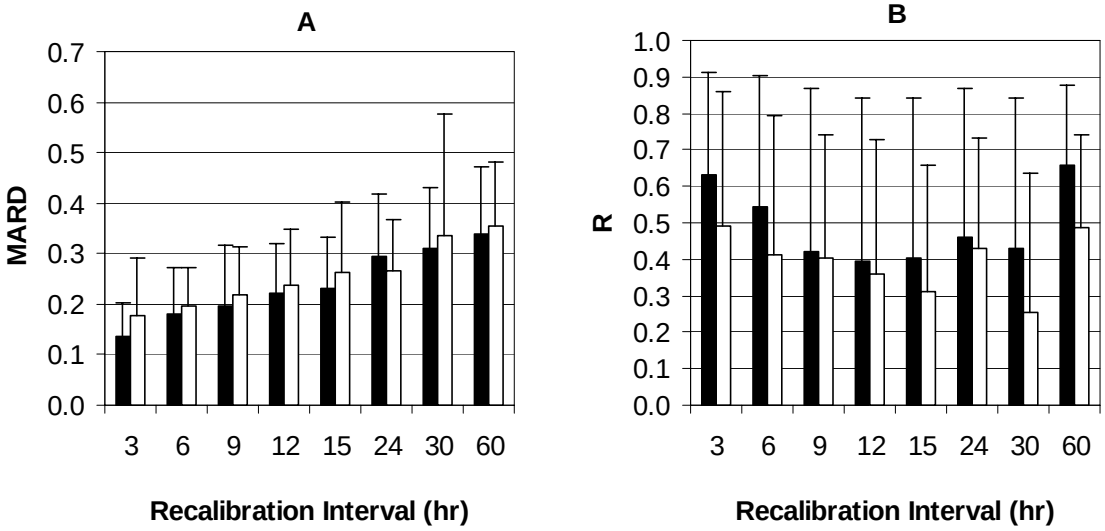


Figure 7: Average MARD (panel A) and R (panel B) values calculated using sensor data paired with arterial reference data (black bars) and venous reference data (white bars) for recalibrations performed every 3, 6, 9, 12, 15, 24, 30 and 60 hours. Error bars represent the SD of the average values.

Discussion

Using MARD and R to determine the appropriate recalibration frequency is not a straight-forward process. The optimal frequency would minimize MARD and maximize R. While increasing the recalibration frequency reduced MARD, it also reduces R initially. The recalibration interval of 6 hours results in an average MARD below 0.2. No recalibration frequency resulted in an average R greater than 0.9.

Combination of Sensor Measurements

Using several glucose sensors at the same time has the potential to improve measurement accuracy and system reliability. For this study, six TGMS sensors were placed on each subject, grouped in two arrays. Each sensor in an array was in close proximity to the other sensors in the array (any particular sensor was, at most, only 10 centimeters away from any other sensor in the array). Two combination schemes were evaluated: the median (*i.e.*, the average of the third and forth ranked values) and the trimmed mean (*i.e.*, the average of the second, third, forth and fifth ranked values) of the 6 sensor blood glucose values.

Purpose

The combination of multiple sensor outputs was investigated to determine if it could improve sensor performance.

Methods

All sensor data was used in the analysis. Sensor data was smoothed with the same FIR filter used in the Recalibration Frequency analysis. Sensor data collected before the 2-hour run-in time was excluded. Filtered sensor blood glucose values, re-calibrated every 6 hours, were combined to produce one measurement per subject per time point. The MARD and R from the two combination schemes (median and trimmed mean) were compared to the values obtained for individual sensors.

Results

The MARD and R values calculated for the median and trimmed mean are listed in Table 8. MARD and R were not calculated for the reference venous measurements from subjects B2 and C2 (refer to Recalibration Frequency analysis for more information). Figure 8 plots the MARD and R for the combination schemes against the range of MARD and R values from individual sensors. Both combination schemes always outperformed the worse individual sensor. In several cases, the median's MARD was lower than best sensor (paired arterial reference for subject A3 and paired venous reference for subjects D2 and D3) and the median's R was greater than the best performing individual sensor (paired arterial reference for subjects B2 and D2 and paired venous reference for subjects D2 and D3). The trimmed mean's MARD was lower than best individual sensor in one case (paired arterial reference for subject A3) and the trimmed mean's R was greater than the best performing individual sensor (paired venous reference for subjects D2).

Table 8: MARD and R values using arterial and venous reference data for combined sensor measures, median and trimmed mean

	Arterial Reference				Venous Reference			
	MARD		R		MARD		R	
Subject	Median	Trimmed Mean	Median	Trimmed Mean	Median	Trimmed Mean	Median	Trimmed Mean
A2	0.113	0.113	0.885	0.885	0.184	0.183	0.682	0.686
A3	0.122	0.124	0.335	0.322	0.157	0.157	0.600	0.598
B2	0.110	0.110	0.877	0.881	n/a	n/a	n/a	n/a
B3	0.170	0.167	0.223	0.235	0.168	0.168	-0.081	-0.086
C2	0.305	0.275	0.645	0.671	n/a	n/a	n/a	n/a
C3	0.116	0.118	0.801	0.796	0.130	0.131	0.811	0.809
D2	0.094	0.097	0.936	0.917	0.139	0.168	0.919	0.912
D3	0.179	0.258	0.620	0.423	0.141	0.177	0.697	0.463
E3	0.222	0.228	-0.420	-0.443	0.235	0.248	-0.187	-0.197
F3	0.111	0.123	0.697	0.623	0.134	0.143	0.519	0.393

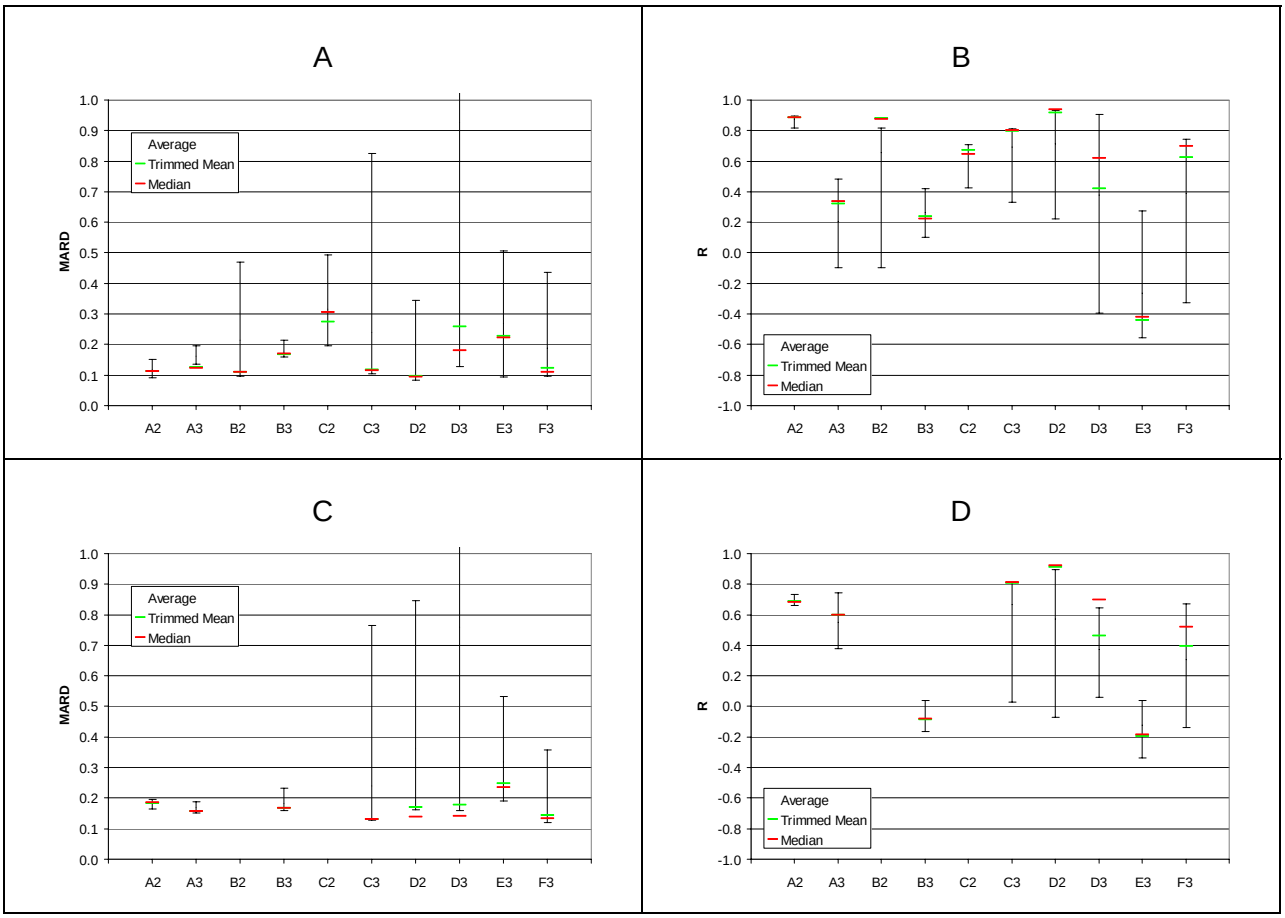


Figure 8: MARD (panels A and C) and R (panels B and D) values calculated for each combination scheme (median and trimmed mean) for each subject. Resulting combined measurements were paired with arterial reference data (panels A and B) and venous reference data (panels C and D). Red and Green bars represent MARD (or R) for the median and trimmed mean, respectively. The vertical black line represents the range of MARD (or R) for the individual sensors for a given subject.

Discussion

The median and trimmed mean produce an estimate of central tendency, which is robust with respect to possible outliers in the data. The median is the most robust measure of location, which is not affected by up to 50% outliers on one side. In our case, it is robust to possibly up to two bad sensors on a high end and two bad sensors on the lower end. The trimmed mean is also robust to outliers because a certain percentage of values is discarded (Here 2 of 6 values are discarded corresponding to 33% of the data at each time point).

Section B

The VGMS sensor was placed in the superior vena cava through a catheter introducer placed in the right internal jugular vein. Each subject received one VGMS in the first five studies. The sensor was not available from the manufacturer for the last five studies. MARD and R were calculated for time-matched sensor/reference pairs (Table 9). Sensor data was calibrated using only the *in vitro* calibration curve. MARD and R reported for subject A3 use sensor data that was truncated after 36 hours at which time the sensor failed. Sensor failure was do to a sudden loss of the reference oxygen electrode signal. This loss was not associated with any change in other measured analytes – the venous pO_2 was stable during the loss. No noteworthy assessment occurred around the loss.

Table 9: MARD and R using arterial, venous and capillary reference data for the five VGMS sensors studied

	Arterial			Venous			Capillary		
Subject	**n**	**MARD**	**R**	**n**	**MARD**	**R**	**n**	**MARD**	**R**
A2	80	0.272	0.679	40	0.434	0.741	-	-	-
A3	90	0.363	0.312	35	0.639	0.292	13	0.305	-0.257
B2	95	0.830	0.695	-	-	-	17	0.876	0.786
B3	82	0.722	0.580	29	0.860	0.548	11	0.734	0.644
C2	45	0.945	0.499	-	-	-	13	0.834	0.281
	78	*0.626*	*0.553*	*35*	*0.644*	*0.527*	*14*	*0.687*	*0.364*
	20	*0.295*	*0.156*	*6*	*0.213*	*0.225*	*3*	*0.261*	*0.465*

Key Research Accomplishments

- 10 patient studies completed
    - 5 studies with both VGMS and TGMS sensors
    - 5 studies with the TGMS sensors only
- Two abstracts presented at the 2006 ASA conference in Chicago, IL
- Abstract accepted for presentation at the 2007 DTM in San Francisco, CA

Reportable Outcomes

Two abstracts analyzing the data from the first subject (patient A2) were accepted and scheduled for a poster discussion presentation at the 2006 Annual Meeting of the American Society of Anesthesiologists. The abstracts, entitled “Continuous Glucose Monitoring in the Perioperative Period” and “Lag Associated with Interstitial Glucose Sensors used in a Diabetic Surgical Patient”, were included in the original final report.

An abstracts analyzing the TGMS sensor data was accepted and scheduled for a poster presentation at the 2007 Diabetes Technology Meeting in San Francisco. The abstract, entitled “The Performance of Subcutaneous Glucose Sensors in Surgical Patients”, is included in the appendix.

Conclusions

Ten of the 60 TGMS sensors did not remain within the subcutaneous space throughout the entire study. In the outpatient setting, the abdomen is the preferred site for implantation for sensors like the TGMS sensor. The choice of the most appropriate placement for these sensors in the inpatient setting may not be a trivial task. If adequate subcutaneous tissue is present in the arm, this may be the most appropriate site for sensor placement.

This technology cannot be dismissed as a possible candidate to monitor glucose levels in hospitalized patients. In select subjects, the TGMS sensors performed exceptionally. With a single calibration, the filtered TGMS sensor outputs for subject A2 had an average MARD of 0.146 ± 0.080 and 0.335 ± 0.286 when paired with arterial and venous reference measurements. With a single calibration, the filtered sensor outputs of the right thigh array for subject D2 had an average MARD of 0.129 ± 0.038 and 0.314 ± 0.076 when paired with arterial and venous reference measurements (whereas the left thigh array dislodged during the study). Conversely, the TGMS sensors inserted in subject E3 had poor correlation with the measured glucose values. Whereas subjects A2 and D2 had the two largest BMI values (as well as the greatest glucose variability) in the study population, subject E3 had the second lowest. Additional research into the relationship between BMI and sensor performance should be considered.

References

1. Hoaglin, D. C., Iglewicz, B., and Tukey, J. W., (1986) “Performance of Some Resistant Rules for Outlier Labeling, ” Journal of the American Statistical Association, 81, 991-999
2. Vonesh, E. F. and Chinchilli, V. M. (1997), Linear and Nonlinear Models for the Analysis of Repeated Measures, New York: Marcel Dekker
3. Yohai VJ. High Breakdown Point and High Efficiency Robust Estimates for Regression. Annals of Statistics 1987; 15: 642-656

Appendices

2007 DTM Abstract: Hipszer B, Chervoneva I, Gratch D, Heitz J, Maguire D, Yeo C, Grunwald Z, Joseph JI. The Performance of Subcutaneous Glucose Sensors in Surgical Patients. Abstract, Diabetes Technology Meeting, October 2007, San Francisco, CA

Appendix: 2007 DTM Abstract

Hipszer B, Chervoneva I, Gratch D, Heitz J, Maguire D, Yeo C, Grunwald Z, Joseph JI. The Performance of Subcutaneous Glucose Sensors in Surgical Patients. Abstract, Diabetes Technology Meeting, October 2007, San Francisco, CA

Title: The Performance of Subcutaneous Glucose Sensors in Surgical Patients

Introduction
Continuous glucose monitoring has the potential to improve glycemic management. Subcutaneous glucose sensors (modified Guardian RT® sensors; Medtronic Diabetes, Northridge, CA) were evaluated in the perioperative period.

Methods
Six non-diabetic (ND) and 4 type 2 diabetic (T2DM) patients undergoing major abdominal surgery participated. Six sensors were inserted into each patient prior to surgery. Reference arterial (and venous) glucose concentrations were measured every 20 (and 60) minutes for up to 60 hours.

Sensor data were filtered and calibrated using a single one-point calibration with a fixed offset after a two-hour run-in period. Pearson correlation coefficient (R) and mean absolute relative difference (MARD) were calculated from paired reference/sensor values. Individual R and MARD were modeled in a linear mixed-effects model and outliers were identified. Statistics were computed from a model based on outlier-free data. Data reported as mean ± SD unless noted.

Results
Nine sensors were excluded as outliers. Duration of arterial and venous sampling averaged 36±10 and 48±10 hours. Arterial and venous glucose averaged 155±48 and 143±51 mg/dl in T2DM and 137±24 and 125±24 mg/dl in ND. For arterial, R values were 0.81 (95% CI: 0.65-0.98) and 0.59 (0.45-0.72) in T2DM and DM. For venous, R values were 0.76 (0.60-0.92) and 0.49 (0.36-0.63) in T2DM and ND. MARD was lower for T2DM (-13%, p=0.142), and decreased as the reference glucose range increased (p=0.019). MARD was 21% (95% CI: 9-34) in T2DM and 34% (24-44) in ND.

Conclusions
T2DM patients had greater glucose variability. R increased, and MARD decreased, as the glucose range increased. However, MARD is also affected the calibration routine. Further analysis using more sophisticated calibration routines, including the default Guardian RT algorithm, is required.

Acknowledgements
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